EXHIBIT 4

Jordan A. Thomas
Labaton Sucharow
140 Broadway
New York, NY 10005

February 10, 2022

Re: Docket Nos. FDA-2021-P-0930 and FDA-2021-P-0967

Dear Mr. Thomas:

This letter responds to your citizen petition received on August 23, 2021 (August Petition), with supplements dated August 30, 2021, September 9, 2021, November 17, 2021, and December 8, 2021 (Docket No. FDA-2021-P-0930) and your citizen petition received on September 1, 2021 (September Petition), with a supplement dated September 9, 2021 (Docket No. FDA-2021-P-0967) (collectively, your Petitions).

Your August Petition describes "grave concerns about the quality and integrity of the laboratory-based studies surrounding this drug candidate and supporting the claims for its efficacy," and requests that the Food and Drug Administration (FDA or Agency):

- halt the current clinical studies of Simufilam (PTI-125) sponsored by Cassava Sciences (NCT04388254 and NCT04994483), pending audits of (1) the publications relied on by Cassava in support of its scientific claims concerning Simufilam; (2) the [investigational new drug application (IND)] for Simulifam's [sic] use in Alzheimer's Disease; and (3) all clinical biomarker studies of Simufilam in Alzheimer's Disease…

- oversee third party reanalysis of all clinical biomarker studies of Simufilam in Alzheimer's disease

(August Petition at 1-2).

You further state that "[t]he ongoing clinical trials should be paused until the satisfactory completion of these investigations" (August Petition at 2).

Similarly, your September Petition describes "grave concerns about the quality and integrity of the laboratory-based studies surrounding this drug candidate and supporting the claims for its efficacy," and requests that FDA:

- halt the new clinical study of Simufilam (PTI-125) sponsored by Cassava Sciences (NCT05026177), pending audits of (1) the publications relied on by Cassava in support of its scientific claims concerning Simufilam; (2) the [IND] for Simulifam's

> [sic] use in Alzheimer's Disease; and (3) all clinical biomarker studies of Simufilam in Alzheimer's Disease; . . .
>
> - oversee third party reanalysis of all clinical biomarker studies of Simufilam in Alzheimer's disease

(September Petition at 1-2).

You further state that "[t]he upcoming clinical trial should be paused until the satisfactory completion of these investigations" [1] (September Petition at 2).

On November 17, 2021, you submitted a third supplement to the August Petition (the Third Supplement) stating that based on increasing evidence of purported wrongdoing, "FDA has a duty to immediately halt the simufilam (PT1-125) clinical trials, conduct a rigorous audit of all the company's research and clinical trial results, and report the agency's findings to interested law enforcement and regulatory authorities" (Third Supplement at 1).

FDA has carefully considered your Petitions and acknowledges the importance of the issues they raise. But as a threshold matter, by their own terms, your Petitions do not purport to set forth all relevant factual information. Rather, you call on FDA to initiate an investigation and fact-finding process. We are denying your Petitions to the extent that they request, through the citizen petition process, that FDA initiate an investigation. Under § 10.30 (21 CFR 10.30), citizen petitions can request that FDA issue, amend, or revoke a regulation or an order, or take or refrain from taking an administrative action,[2] and are to be resolved based on information in the administrative record.[3] An investigation is not an administrative action, and, as your Petitions implicitly acknowledge, investigations necessarily require fact finding beyond what is presented in the current administrative record.

Moreover, issuing a response to your requests would appear to require FDA to publicly disclose information about an investigational new drug that, by law, FDA generally cannot publicly disclose. The Trade Secrets Act, 18 U.S.C. 1905, prohibits the disclosure of confidential commercial information unless doing so is authorized by law. FDA's regulations regarding confidential commercial information provide that if the existence of an unapproved application has not previously been publicly disclosed, "no data or information in the application . . . is available for public disclosure."[4] In addition, FDA's regulations provide that "the existence of an investigational new drug application will not be disclosed by FDA unless it has previously been publicly disclosed or acknowledged."[5] Thus, if the product sponsor has not previously

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[1] In your September 9, 2021, supplements to the August Petition and the September Petition, you also "respectfully recommend rescinding the recently announced [Special Protocol Assessment] for Simufilam" (September 9, 2021, supplement at 8).

[2] See § 10.30(b)(3).

[3] See § 10.30(j).

[4] § 314.430(c) (21 CFR 314.430(c)).

[5] 21 CFR 312.130(a).

made public the filing of an IND, FDA will not disclose the IND's existence. Nor will FDA disclose any information submitted as part of the IND: the application "includes all data and information submitted with or incorporated by reference in any application or abbreviated application, including investigational new drug applications."[6] If the sponsor has already disclosed the existence of an IND for a not-yet-approved product, FDA may confirm the existence of the IND.[7] However, FDA still will not make any "data or information contained in the application . . . available for public disclosure before the agency sends an approval letter," aside from narrow exceptions that are not relevant here.[8] Accordingly, restrictions on disclosure of nonpublic information contained in an IND file apply both when a sponsor has already disclosed the existence of an IND, and when a sponsor has not.

With respect to your supplemental request that FDA report findings "to interested law enforcement and regulatory authorities," such a request is similarly not amenable to the citizen petition process. Decisions regarding enforcement actions are made on a case-by-case basis and are within the discretion of FDA. Requests for the Agency to initiate enforcement action and related regulatory activity are expressly excluded from the scope of FDA's citizen petition procedures.[9]

We take the issues you raise seriously. Please note that your Petitions are being denied solely on the grounds that your requests are not the appropriate subject of a citizen petition. This response does not represent a decision by the Agency to take or refrain from taking any action relating to the subject matter of your Petitions.

Sincerely,

Patrizia A. Cavazzoni -S

Digitally signed by Patrizia A. Cavazzoni -S
Date: 2022.02.09 19:26:42 -05'00'

Patrizia Cavazzoni, M.D.
Director
Center for Drug Evaluation and Research

[6] § 314.430(a).

[7] § 314.430(b).

[8] § 314.430(d)(1).

[9] § 10.30(k).